DECLARATION OF LEONARD A. SMITH

I Leonard A. Smith declare as follows:

1. I am a citizen of the Unites States and presently reside in Clarksburg, Maryland.

2. I am over the age of twenty one, competent to testify in a court of law, and could and would testify to the matters set forth below before the United States Patent and Trademark Office, if required to do so.

3. I understand that this declaration will be used to assist prosecution of one or more of the following related, pending patent applications:
(1) United States patent application serial number 10/933,723, including to assist to overcome a rejection in the June 29, 2007 office action in serial number 10/933,723;
(2) United States patent application serial number 10/443,593, including to assist to overcome a rejection in an office action in serial number 10/443, 593;
(3) United States patent application serial number 10/726,904, including to assist to overcome a rejection in an office action in serial number 10/726,904;
(4) United States patent application serial number 10/460,898, including to assist to overcome a rejection in the June 28, 2007 office action in serial number 10/460,898, and;
(5) United States patent application serial number 10/461,829 including to assist to overcome a rejection in an office action in serial number 10/461,829.

4. I graduated from the University of New Hampshire (Durham, NH) in 1972 with the degree of bachelor of arts in chemistry and zoology (dual major), and in 1978 I received a Ph.D degree from Georgetown University, Washington, D.C. for advanced studies in biochemistry. My Ph.D thesis was for work on bacterial enzymes.

5. I am the recipient of the 2007 Joel M. Dalrymple Award for outstanding contributions and achievements in the discovery and development of biodefense vaccines, recipient of the 2007 Scientist of the Year Award from the Defense Threat Reduction Agency, as well as of the Order of Military Medical Merit Award. Additionally, I am a member of the faculty of the Neurotoxin Institute (NYC). Furthermore, I am on the editiorial board of numerous peer reviewed journals, including The Botulinum Journal; Expert Reviews in Vaccines; The Protein Journal, and; The Journal of Industrial Microbiology and Biotechnology.

6. I have served as an advisor or as an expert consultant to the Institute of Medicine, the National Research Counsel, the National Institute of Allergy and Infectitious Diseases ("NIAID"), the Deparment of Health and Human Services, the Department of Homeland Security, and the Defense Threat Reduction Agency Joint Science and Technology Office for Chemical-Biological Defense, and I am a member of the NIAID-sponsored Working Group for the development of small molecule inhibitors of botulinum toxin.

7. I have been employed by the United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland ("USAMRIID") since 1982. I have had oversight of all scientific activities at USAMRIID. I am currently Chief of the Department of Molecular Biology, Integrated Toxicology Division at USAMRIID (and Supervisory Research Chemist), a position I have held since 1995. Prior to that I was Supervisory Research Chemist in the USAMRIID Departments of Immunology and Molecular Biology, Division of Toxinology and Aerobiology.

8. I have extensive experience in the discovery and early and advanced stage development of vaccines and therapeutic drug products, including those involving botulinum toxin. In particular, I have extensive experience characterizing and formulating the neurotoxic component of a botulinum toxin (the approximately 150 kDa active part of a botulinum toxin complex, hereafter called "the neurotoxic component") beginning in about 1985. See eg Smith, Leonard L., et al., *Photoaffinity labeling of*

botulinum neurotoxin by azido-ATP, pages 33-39 of Falmagne P., et al editors, Bacterial Protein Toxins, Gustav Fisher, New York (1986) (copy attached as Exhibit A).

9. A significant aspect of my work at USAMRIID has involved production, formulation, and characterization of native botulinum toxin and recombinant neurotoxin component fragments and protease-inactive botulinum neurotoxin holotoxins, for example to develop human vaccines against the neurotoxic component. See eg my publications: *Development of recombinant vaccines for botulinum neurotoxin*, Toxicon 1998 Nov;36(11):1539-1548; *Expression, purification, and characterization of Clostridium botulinum type B light chain,* Protein Expr and Purif 2006;46(2):256-267; *Roads from vaccines to therapies,* Mov Disord 2004 Mar;19(Suppl 8):S48-52; *Cell bank characterization and fermentation optimization for production of recombinant heavy chain C-terminal fragment of botulinum neurotoxin serotype E,* J Biotechnol 2007;127(3):462-47; *Evaluation of a botulinum fragment C-based ELISA for measuring the humoral immune response in primates*, Biologicals 2003 Mar;31(1):17-24, and; *Evaluation of the therapeutic usefulness of botulinum Neurotoxin B, C1, E, and F compared with the long lasting type A*, J Biol Chem 2003 Jan;278(2):1363-1371, copies of which six publications are attached as Exhibits B to G.

10. Several of the vaccines to portions of the neurotoxic component I developed or which were developed under my supervision and guidance are currently being tested in the United States in FDA approved human clinical trials. Development of these vaccines required production and purification of the receptor binding domain of the neurotoxic component from a botulinum toxin which is then administered to human subjects. A new vaccine under development in my laboratory is a recombinant protease-deactivated holotoxin (devoid of complex binding proteins). This type A atoxic botulinum neurotoxin is easily produced and purified from yeast, is highly stable in different buffers and pH ranges, is stable in liquid formulations at room temperature and 4^{0}C, is stable frozen, is stable to freeze-thaw cycles, and elicits protective immunity against all known subtypes of botulinum neurotoxin serotype A toxins.

11. By training and experience I am an expert in the properties of the neurotoxic component, including the protein biochemistry of the neurotoxic component and all of its recombinant domains.

12. I have been retained as a consultant by Allergan Inc. ("Allergan") with regard to various botulinum toxin matters since 2002. Allergan is the assignee of the patent applications cited in paragraph 3 above, as well as of their common parent application, U.S. application serial number 08/173,996, which has a filing date of December 28, 1993 and which is referred to hereafter as "the '996 application".

13. I have carefully read Schantz E., et al., *Properties and use of botulinum toxin and other microbial neurotoxins in medicine*, Microbiol Rev 1992 Mar;56(1):80-99 (referred to hereafter as "Schantz 1992"), a copy of which is attached as Exhibit H.

14. Schantz 1992 makes several statements which can be construed as indicating that the neurotoxic component has little or no clinical utility or, synonomously, that the neurotoxic component would be unlikely to be used for therapeutic purposes in humans. Thus, Schantz 1992 states on page 82:

"The nontoxic proteins bound to the neurotoxin (i.e. to the neurotoxic component) apparantly play an important role in maintaining the toxic shape of the neurotoxin...Because of its lability the neurotoxin (i.e. the neurotoxic component) is not practical for medical applications." (text in parenthesis added).

Schantz 1992 also states on page 89 in the paragraph entitled "**Clinical use of pure neurotoxin compared with toxin complexes**" (emphasis in original) that with regard to the neurotoxin component "...it is unlikely these will be used in a clinical setting" because the neurotoxic component is "inactivated on dilution, formulation and drying".

15. There is no doubt in my mind and it is my opinion that the statements in Schantz 1992 that the neurotoxic component is "not practical for medical applications" and that

the neurotoxic component "is unlikely..(to).. be used in a clinical setting" are clearly wrong.

I base my opinion on the following facts:

(a) there is no data or experiment presented in Schantz 1992 to support his opinion that the neurotoxic component is not practical for medical applications or that the neurotoxic component is unlikely to be used in a clinical setting. That is, there is no data in Schantz 1992 showing that the neurotoxic component cannot be prepared as a stable formulation useful to treat a human disorder. Hence, the referred to statements in Schantz 1992 are mere conjecture and unsupported opinion statements.

(b) The statements made in Schantz 1992 regarding clinical unsuitability of the neurotoxic component of a botulinum toxin has been challenged in the literature. See eg page 31 of DasGupta B., *Structures of botulium Neurotoxin, its functional domains, and perspectives on the crystalline type A toxin*, pages 15-39 in Jankovic J. et al., Therapy with botulinum toxin, Marcel Dekker, Inc., New York (1994) (copy attached as Exhibit I):

"The rationale for clinical use of the impure type A NT ("neurotoxin") (about 80% of protein in the crystallized complex is nonneurotoxic protein) is that the nonneurotoxic proteins 'bound to the neurotoxin apparantly play an important role in maintaining the toxic shape of the neurotoxin' (quoting from Schantz 1992)...'an important point regarding the use of purified neurotoxin (i.e. the neurotoxic component) besides its instability is the fact that it cannot be prepared with constant composition and activity' (quoting from Schantz E. et al, *Use of crystalline type botulinum toxin in medical research*, pages 143-150 of Lewis GE editor, Biomedical aspects of botulism, Academic Press, New York (1981). This is not true, and this prevailing view needs rectification." (emphasis added).

(c) Additionally, after the March 1992 publication date of Schantz 1992 but before the December 1993 filing date of the '996 application it was known that a storage stable formulation of the neurotoxic component could be administered to various mammal species with physiological effect. Thus, in Lamanna, C., *Thoughts on action of*

botulinum toxin suggested by reversibility of heart effects, pages 333-335 in Botulinum and Tetanus Neurotoxins, edited by Dasgupta B., Plenum Press, New York (1993) (copy attached as Exhbit J) it is stated on page 333: "Type A hemagglutinin-free toxin causes electrocardiographic changes and a decreased heart rate (bradycardia) within minutes of injection of the toxin in rodents and dogs, the species studied". "Type A hemagglutinin-free toxin" is synonomous with the neurotoxic component. The Lamanna 1993 publication quoted from above cites to the author's earlier publication Lamanna C. et al., *Cardiac effects of botulinal toxin*, Arch Int Pharmacodyn Therap 1988; 293: 69-83 (copy attached as Exhibit K) in which is it disclosed that mice, rats, rabbits and dogs (see the Abstract of Exhibit K) were intravenously injected with identical storage stable formulations of both the botulinum toxin complex (page 70: "Crystalline type A toxin that had hemagglutinin as a constituent") and the neurotoxin component (page 70: "type A toxin free of hemagglutinin") both formulated in exactly the same way: "The toxins were dissolved in a sterilized phosphate-0.2% gelatin buffer (pH 6.2-6.7) for storage and i.v. injection" (page 70).

It is clear that the the Lamanna 1993 publication discloses preparation and administration of a storage stable formulation of the neurotoxic component because Lamanna 1993 states on page 72: "The crystalline toxin and the hemagglutinin-free toxin had the same qualitative effects on the heart...The crystalline toxin has a molecular weight of 900,000...while the hemagglutinin-free toxin has a molecular weight of 150,000....".

(d) Furthermore, essentially concurrent with the December 1993 filing date of the '996 application it was known that the neurotoxic component could be diluted, formulated and dried to prepare an active, potent formulation of the neurotoxic component. Significantly, it was also known that the neurotoxic component can be formulated and the botulinum toxin complex can be formulated, both using exactly the same techniques and exactly the same reagents, to provide two formulations which have at least equal clinical efficasy. In fact, it was known that the neurotoxic component formulation (made using exactly the same techniques and exactly the same reagents used to make the

botulinum toxin complex formulation) can have superior clinical effectiveness as compared to the clinical effectvieness of the botulinum toxin formulation. Thus, the Ph.D thesis entitled *Characterization and stabilization of clostridium botulinum neurotoxin* by Michael C. Goodnough, published by the University of Wisconsin, March 10, 1994 (copy attached as Exhbit L) clearly states that formulations of the neurotoxic component suitable for medical use can be prepared using the same lyophilization (freeze drying) process used for preparing a botulnium toxin complex for medical use, and using the same stabilizing excipient (albumin) used to stabilize the botulinum toxin complex.

The following are excerpts from the published Goodnough Ph.D thesis:

A. "In this research, I have addressed issues related to the quality of botulinum toxins for medical use" (page v).

B. "Full recovery of type A and B toxin complexes as well as the purified ca. 150 kDa toxin molecule was obtained...". (page vi). See also page 118: "Recovery of toxicity following lyophilization of type A and B toxin complex as well as the purified ca. 150 kDa toxin molecules was obtained...".

C. "Type A neurotoxin was purified from the associated non-toxic proteins of the complex...Toxin was seperated from the non-toxic proteins of the complex..." (page 125). See also page 130: "Type A neurotoxin purified from the non-toxic components of the complex...".

D. "Purified type A neurotoxin and crystalline type A toxin complex were used in seperate experiments" (page 141).

E. "Type B neurotoxin was purified from the complex..." (page 127).

F. "Some vials of lyophilized type A neurotoxin and type A toxin complex were stored... (page 128).

G. "In further efforts to reduce the amount of neurotoxin needed to yield 100 LD_{50}/vial following lyophilization, purified type A and B neurotoxins were dried in the presence of serum albumin. Although the neurotoxins are more labile that the complex, recoveries on drying were similar to those obtained with the complexes (Table 3)...Recoveries of type A and B neurotoxin following lyophilization were high (≥80% of pre-lyophilized starting values)..." (page 137).

H. "Recovery of activity following lyophilization of purified type A and B neurotoxin does not seem to be dependant on the presence of the non-toxic binding proteins of the complex as a high percentage of toxin activity was recovered using the same formulation as that used for the type A and B toxin complexes." (page 142).

I. "Our results indicate that purified type A neurotoxin is more stable at elevated temperatures than type A complex when lyophilized in the three excipient systems tested." (page 144).

J. "A toxin standard was prepared using purified type A neurotoxin in 50 mM sodium acetate, 2 mg/ml gelatin (Difco), 3 mg/ml bovine serum albumin (Sigma), pH 4.2, according to the method of Schantz and Kautter (1978)."

16. The excerpts above from the published Goodnough Ph.D thesis make it clear that a stable and effective formulation of the neurotoxic component can be prepared in the same manner that a stable and effective formulation of a botulinum toxin complex can be prepared, that is that the contrary statements in Schantz 1992 are wrong. Thus, the person of ordinary skill in the field (i.e. a physician of ordinary ability with knowledge of or experience using a botulinum toxin, referred to hereafter as the "Physician") could obtain, formulate and clinically use a potent and effective neurotoxic component formulation prepared by using the same reagents and the same dilution, drying and

reconstitution techniques known for preparing and using a clinically effective botulinum toxin complex formulation.

17. Furthermore, it is my opinion that the '996 application, in light of the art set forth above, clearly and explicitly discloses how the Physician can therapeutically use the neurotoxic component to effectively treat patients, that is how to use the neurotoxic component in a clinical setting.

I base this opinion on the following facts:

(a) the '996 application at page 3, lines 5-24 of the '996 application states that there is a neurotoxic component of a botulinum toxin, that the neurotoxic component has a molecular weight of about 150 kD, that the neurotoxic component is responsible for the toxic properties of a botulinum toxin and that the neurotoxic component (in either it's single or dichain forms) is "useful in the method of the present invention" thereby directly and immediately stating that the neurotoxic component can be used to treat the various disorders set forth in the '996 application.

(b) the '996 application discloses how to prepare a therapeutically effective formulation of the neurotoxic component. For example page 7, line 17, continuing to page 8, line 10 of the '996 application (set forth below) discloses how to formulate, stabilize and reconstutute the neurotoxic component, using the same process used to formulate, stabilze and reconstitute the botulinum toxin complex:

"The toxin can be presented as a sterile pyrogen-free aqueous solution or dispersion and as a sterile powder for reconstitution into a sterile solution or dispersion.

Where desired, tonicity adjusting agents such as sodium chloride, glycerol and various sugars can be added. Stabilizers such as human serum albumin may also be included. The formulation may be preserved by means of a suitable pharmaceutically acceptable preservative such as a paraben, although preferably it is unpreserved.

It is preferred that the toxin is formulated in unit dosage form; for example, it can be provided as a sterile solution in a vial or as a vial or sachet containing a lyophilized powder for reconstitiuting a suitable vehicle such as saline for injection.

In one embodiment, the Botulinum toxin is formulated in a solution containing saline and pasteurized human serum albumin, which stabilizes the toxin and minimizes loss through non-specific adsorption. The solution is sterile filtered (0.2 micron filter), filled into individual vials and then vacuum-dried to give a sterile lyophilized powder. In use, the powder can be reconstituted by the addition of sterile upreserved normal saline (sodium chloride 0.9% for injection)."

(c) the '996 application discloses how to administer the neurotoxic component to a patient. See eg page 7, lines 11-17 ("Preferably, the toxin is administered by means of intramuscular injection..."); page 8, lines 11-16 ("The dose of toxin administered to the patient will depend upon the severity of the condition..."), and; page 9, lines 25, continuing to page 10, line 13 ("Before injecting any muscle group, careful consideration is given to the anatomy of the muscle group..."). Additionally, each of the thirty three Examples on pages 10 to 20 of the '996 application disclose how to use either the neurotoxic component or a botulinum toxin complex in a clinical setting because although the phrase "botulinum toxin" is used in the Examples we are told on page 3 of the '996 application that the neurotoxic component is "useful in the present invention". Hence, the Examples of the invention in the '996 application obviously include administration of just the neurotoxic component in these clinical use examples. Thus, the '996 application undoubtly discloses that the neurotoxic component is clinically effective.

18. Thus, it is my opinion that the '996 application teaches a Physician how to formulate a clinically effective formulation of the neurotoxic component, and as well how to administer to patients a therapeutically effective neurotoxic component formulation.

19. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of

Title 18 of the United States Code and that such willful false statements may jeopardize the validity and/or enforceability of the present patent application or any patent issuing thereon.

Executed this 20th day of November 2007 at Fort Detrick, Maryland.

Leonard A. Smith

Leonard A. Smith